

AD\_\_\_\_\_

Award Number: W81XWH-09-2-0184

TITLE: Near-Infrared Spectroscopy to Reduce Prophylactic Fasciotomies for and Missed Cases of Acute Compartment Syndrome in Soldiers Injured in OEF/OIF

PRINCIPAL INVESTIGATOR: LTC Brett Freedman, MD

CONTRACTING ORGANIZATION: The Geneva Foundation

Tacoma, WA 98402

REPORT DATE: October 2014

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:

☒ Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
1. REPORT DATE (DD-MM-YYYY) October 2014		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 30 Sep 2013 - 31 Aug 2014	
4. TITLE AND SUBTITLE Near-Infrared Spectroscopy to Reduce Prophylactic Fasciotomies for and Missed Cases of Acute Compartment Syndrome in Soldiers Injured in OEF/OIF				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-09-2-0184	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Brett Freedman - Principal Investigator  email: brett.freedman@amedd.army.mil				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)  The Geneva Foundation  Tacoma, WA 98402				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The research project is a three-part project to validate the accuracy and reliability of a specific NIRS sensor (Equanox, Nonin, Inc, Plymouth, MN) in diagnosing acute compartment syndrome in injured combat soldiers. Part 1 is a series of two observational studies, the first of which was completed at Landstuhl Regional Medical Center during year 1. The second clinical study was originally planned to be conducted in theatre in Afghanistan and Iraq, but had to be transitioned to a FDA-regulated study conducted under an abbreviated IDE within the USA. This study was established in Period 3 and completed in Period 4. Part 2 of the project involves animal studies to address issues raised in clinical testing and furthering understanding of NIRS response to ACS. Three informative animal studies were completed and the results of which have been presented over the grant period. Part 3 of this project is the translation of the current technology into a validated, FDA approvable format. Data collected in Parts 1 and 2 will be used as the basis for developing a NIRS-based diagnostic algorithm that will be validated in a subsequent clinical trial following the completion of this grant.					
15. SUBJECT TERMS Near Infra-Red Spectroscopy, acute compartment syndrome					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	21	19b. TELEPHONE NUMBER (include area code)

## Table of Contents

INTRODUCTION	4
BODY	5
<u>Task 1: Human Use Study – Phase 1</u>	<u>5</u>
<u>Task 2: Human Use Study – Phase 2</u>	<u>5</u>
<u>Task 3: Animal Use Study – Originally-Planned Porcine Study</u>	<u>6</u>
<u>Task 4: Reduction to Practice and FDA Approval Process</u>	<u>7</u>
<u>Task 5: Coordination Between Study Sites</u>	<u>8</u>
<u>Task 6: Future Research Endeavors</u>	<u>8</u>
<u>PROBLEM AREAS</u>	<u>9</u>
<u>KEY RESEARCH ACCOMPLISHMENTS</u>	<u>9</u>
<u>REPORTABLE OUTCOMES</u>	<u>9</u>
<u>CONCLUSIONS</u>	<u>10</u>
<u>REFERENCES</u>	<u>10</u>
<u>APPENDICES</u>	<u>10</u>

## **INTRODUCTION**

The research covered under this award was a three-part project planned to be conducted over three years to validate the accuracy and reliability of using Near Infrared Spectroscopy (NIRS) to diagnose acute compartment syndrome (ACS) in combat soldiers and civilians suffering high energy trauma to the lower extremities. Part 1 was two clinical observational studies. The first part (Phase I) was conducted at Landstuhl Regional Medical Center and was started in the first year of this award and completed on time and on budget. The second study (Phase 2) was originally planned to be conducted in theater at Level III CSHs in Afghanistan and Iraq with support from the Joint Combat Casualty Research Team (JC2RT) and a researcher specifically deployed to lead this study in-theater. However, during the protocol review process, USAMRMC petitioned for a pre-IDE determination from the FDA, and it was decided that the study needed to be conducted as an FDA-regulated study (with “abbreviated requirements”), and was transitioned to three civilian hospitals in the state of Georgia. This transition caused over 12 months delay in initiating the study, as described in a previous annual report. Because of this delay, we were granted a funded-extension for this award into a fourth year. The fourth year proved fruitful and during that time the Phase 2 study was completed, marking successful completion of the original tasks outlined in this grant’s original Statement of Work. Period 5 has been the period of data cleaning and exploratory analysis of the data collected throughout this grant period. The hurdles needed to complete this task, mean there is still work to be done in this area, which is outlined in this annual report.

Part 2 (Task 3) of this award used porcine models of ACS to further evaluate and validate the clinical utility of using continuous NIRS monitoring to diagnose ACS. The initial experiments using albumin infusion and contusion/albumin infusions models for inducing ACS were successfully completed on target by the end of the second year of this grant. These studies demonstrated that NIRS measurement of hemoglobin oxygen saturation in the tibial compartment provided reliable and sensitive correlation to increases and decreases in intra-compartment pressure and intra-compartment perfusion pressure. In year 3, we built on the success of the animal experiments by employing a second model of tibial compartment syndrome, which uses an inflatable balloon to increase intra-compartment pressure. This model was originally conceived in the US Army Institute of Surgical Research. This demonstrated that NIRS accurately detected a critical hypoperfusion that occurs in the setting of ACS. In the controlled state of an animal model, our series of studies built on prior knowledge to provide compelling evidence that NIRS can serve as an accurate and reliable noninvasive means for diagnosing ACS. In the final year, we have (under a no-cost extension for the UGA sub-award) completed animal testing to evaluate the NIRS data obtained when ACS is “missed” or delayed in diagnosis, which is known to be a clinically devastating occurrence. This data is currently being cleaned and analyzed by the UGA research team. In short, our animal testing and that in existence makes us confident that NIRS can accurately monitor the physiological states associated with severe leg injury and ACS, in the controlled setting of an animal model.

The final part of this project (Tasks 4 – 6) included the translation of the current technology into a proven means for detecting the presence of critical hypoperfusion of the leg compartments indicative of acute compartment syndrome. The data collected in our Phase 1 and 2 clinical studies and the animal studies has been and will be used to optimize the technology, develop a decision support algorithm and ultimately form the basis for a subsequent clinical trial to validate this algorithm and lead to the first FDA indicated diagnostic device for ACS. The current FDA approved indication for the NIRS device used in our clinical studies (the Nonin Equanox™ 7600 oximeter) is for monitoring regional tissue oxygenation. This device has been validated and is currently marketed as a means for monitoring for altered states of perfusion in normal (i.e. not traumatically injured, specifically cerebral) tissue. Our research and development initiative has pushed this technology to its limits, by seeking to monitor altered perfusion states in abnormal (i.e. traumatically injured) somatic tissue. In

Period 4, our industry partner and this research team sought to identify areas to improve this technology in the reduction to practice of an ACS diagnostic device. The FDA indication we ultimately will seek to develop, submit and defend using the results of the clinical and animal studies conducted under this grant and the study to follow is a diagnostic and/or decision support indication such that the device can be approved to provide information that directly impacts clinical decision-making for patients at risk of ACS. This function will meet the critical unmet need in combat casualty care originally identified in our grant proposal.

## **BODY**

The primary goal of work conducted in Period 5 was to close-out enrollment for the Phase 2 clinical study and begin data cleaning and analysis. At the conclusion of the previous period (Sep 30, 2014), enrollment had been completed at all three sites, and we were awaiting a close-out visit from the study monitor. At the conclusion of the current period enrollment has been closed and data management and analysis are underway.

### **TASK 1: Human Use Study – Phase 1**

1a – g: All tasks completed on time and within budget in Periods 1 and 2

### **TASK 2: Human Use Study – Phase 2**

2a – c: Tasks completed in Period 2

#### **2d: Conduct Phase 2 Prospective Observational Study**

Tasks completed in Period 4.

#### **2e: Analyze Data, Provider Feedback**

Data cleaning and analysis has been the primary work of Period 5 and abstract / manuscript preparation for public presentation of study results will be undertaken in the time remaining in the overall grant period. The amount of data collected in this study is enormous as it includes longitudinal NIRS measurements taken every 3 seconds for each patient over a 24 – 48 hour period. A complete data analysis for public presentation of study results was on hold until all data was entered and cleaned by the CRO, which was completed in the second quarter of this period.

The major accomplishment of this period has been the initiation of exploratory data analysis. At this early point in an exploratory and primarily visual analysis of the NIRS data, we have already seen some promising trends, including the contralateral leg as a good control in critically ill patients (our cohort 1 sub-group) and nice sections of complete longitudinal data indicating crossover from hyperemia to hypo-perfused states in the setting of confirmed ACS. Basic statistical analyses have begun in preparation for the more sophisticated testing and highly qualified statistical consultants have been identified to assist in carrying out the statistical work. This complex analysis is in its infancy, but will continue through the end of the grant to produce a more in-depth description of ACS development using NIRS technology. In order to realize this goal a 7-month no-cost extension was requested, and is currently under review, to extend the grant period through 31 March 2015.

## 2f: Present and Publish Results of Phase 2 Study

Not due until completion of the Phase 2 study, planned for the second half of Year 4.

The team has prepared several manuscripts this period. The results of the skin pigmentation and ambient light studies (reported in the Period 4 annual report) are now in the final stages of revision and will be submitted shortly. One article reporting NIRS capabilities in the obese, is currently under review (data also reported in the previous annual report) and we are awaiting a decision.

The results of the study entitled *Near Infrared Spectroscopy in the Sub-Acute Setting of Lower Extremity Trauma* were submitted as an abstract to the Military Health System Research Symposium (MHSRS), and was accepted in the third quarter of this period for presentation at the 2014 Annual Meeting.

The current state of our research, as well as the proposed next-step, prospective study, were presented by Dr. Freedman and Dr. Shuler to Col Rasmussen, Dwayne Taliaferro, Rick Kenyon and other representatives via teleconference this period. The presentation included the results of all the small-scale clinic studies performed at the Athens site, internal analyses of missing NIRS data and possible solutions to this issue, results of the first-look exploratory analysis of the Phase 2 clinical data, and an outline of the prospective, diagnostic study that has been planned as a follow-on. An updated version of this presentation was provided to key leaders from CCCRP, USAMMA and USAMRAA at the 2014 Military Health System Research Symposium in Ft. Lauderdale on 19 August. A copy of this presentation is included with this report as **Appendix 1**.

## **TASK 3: Animal Use Study**

### 3a: Created UGA IACUC Protocol Application for Animal Studies

Task completed in Period 4.

### 3b: Obtain UGA IACUC and USAMRMC ACURO Approvals for Second Study

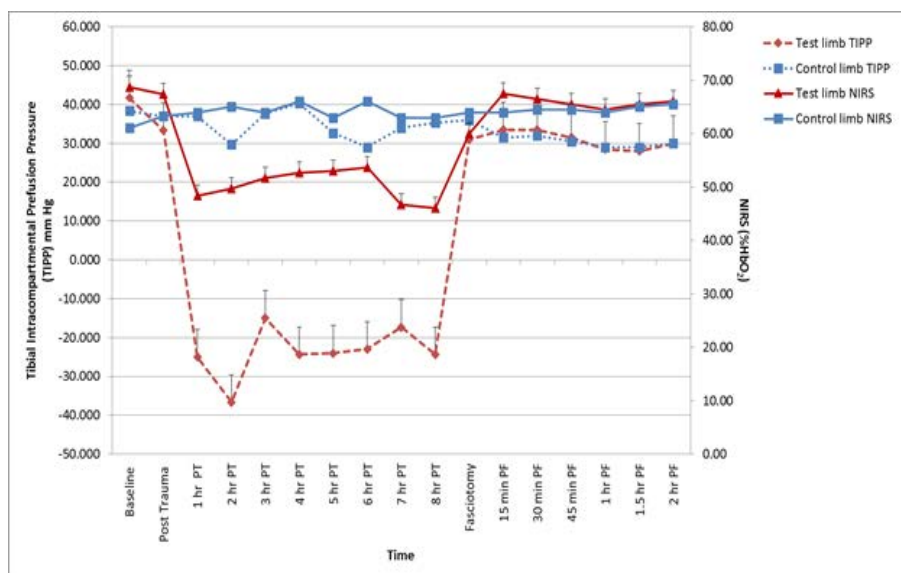
Task completed in Period 4.

### 3c and d: Initiate and Conduct Animal Studies

All studies completed by the end of Period 4.

### 3e and f: Analyze Data and Prepare for Presentation and Publication

The abstract entitled, *Correlation of NIRS and histological muscle damage in a prolonged trauma/infusion model of extremity compartment syndrome (ECS) – assessing NIRS ability to detect the clinical consequence of delayed ECS*, was submitted for presentation at the 2015 meeting of the Orthopedic Research Society this period and we are awaiting a decision. The purpose of the study was to evaluate the correlation between NIRS and histological muscle damage in a prolonged version of our trauma/infusion model of ECS, to understand the NIRS response to delayed/missed ECS. This validated acute trauma model provides evidence that prolonged depression in NIRS values (i.e. hypoperfusion) correlates to muscle damage in the delayed/missed ECS state (see **Figure 1** below). Extended ischemia cannot be performed in humans, but is a serious clinical condition that occurs. This study demonstrates NIRS values are consistently diagnostic of ECS even in the setting of extended ischemia with subsequent muscle necrosis. Counter-intuitively, more necrosis and cell damage occurred after fasciotomy, presumably due to reperfusion, compared to damage at the end of the ischemic period.



**Figure 1:** As expected significant negative correlations of TICP and NIRS, positive correlations of TIPP and NIRS were observed

The veterinary team is in the process of writing the final two manuscripts (results from studies 2 and 3) pending additional assay and statistical results.

#### **TASK 4: Reduction to Practice and FDA Approval Process**

4a: Finalize product development relationships between Nonin, Inc and J+M Shuler – Completed in Year 2

4b: Begin reduction to practice process – Completed in Period 4. The process of reducing to practice technological solutions to the clinical hurdles we have identified for using NIRS to detect ACS has “begun”, but it continues. This is an ongoing work that will transcend this grant period.

4c: Produce final prototype for use in completion of Phase 1, all of Phase 2 and the investigational clinical study to be supported by a future grant – Ongoing

In our earlier annual reports, based on our experience to date at the time, we had declared that the NIRS technology is mature and ideal for our intended indication, and that we had the final prototype. However, in view of the missing signal errors we have encountered in our Phase 2 clinical study completed last period, it is clear that there are some unexpected challenges to using NIRS on traumatized tissue. Some of the challenges were user related. The maturation of our research team into the world’s leading users of NIRS technology in the setting of severe leg injury has allowed us to overcome many of the data acquisition issues; however, despite excellent and perfected technique, some issues remain in some patients regarding missing signal errors. Our series of clinical studies to evaluate co-factors like skin color, fat depth, depth of the muscle compartments (which are always <1-3cm from the skin surface), swelling from trauma and the impact of ambient light on NIRS readings has all informed the process for identifying a solution. This work has confirmed that the base technology is completely capable of monitoring the muscle compartments of all people of any skin color or body habitus in any ambient light environment. The remaining technological gap is seen in monitoring injured muscle. In some injured muscle compartments there is increased absorption of NIR light such that the amount reflected back to the sensor falls below the sensor’s sensitivity. Nonin developed a prototype sensor with larger photoreceptive diodes, which mitigated some but not all of this issue. There are other modifications that are being evaluated to improve monitoring of rSO<sub>2</sub> in traumatized tissue, such as increasing NIR light emission and altering the raw data transformation

algorithm. The 7600 oximeter itself fits the intended use; although increasing the number of ports per machine would be make it more functional.

4d: Respond to provider feedback re: functionality and industrial design – Completed

In our experience with the 7600 oximeter, the only two significant physical improvements needed are:

1. The addition of more ports to a machine, so that a patient can be monitored by a single machine, and
2. “horse-tailing” of leads, such that four (or more) sensors connect via a short cable (one foot) to a common trunk cable that runs to the device. This will cut down on the cable clutter in the current configuration that has led to subjects withdrawing from the study.

**TASK 5: Coordination between study sites**

5a: Bi-annual collaborators meeting – Ongoing

Given the transition from LRMC as a research site for the Phase 2 clinical study, to the Atlanta area, we have increased on-site visits to 3/year.

5b: Conduct weekly VTC (Telcon) for LRMC/J+M Shuler, and OIF/OEF during Phase 2 – No longer required since Phase 2 study is not being conducted in Georgia and not at LRMC.

5c: Rapid interpretation of weakness in the design and function of sequential NIRS pad prototypes and NIRS monitoring algorithms – Ongoing

The device is in a state where it is and has been fully ready for testing in our studies. It will probably undergo some minor physical improvements with time. The major improvement will be the design and validation of a diagnostic algorithm based on NIRS values. This process is ongoing and will continue past our grant period. This process will ultimately require validation in a prospective interventional trial.

5d: Coordinate response to FDA requests for information during approval process – Completed.

LTC David Shoemaker, Marieann Brill and “Decision Gate” were all involved in USAMMDA’s sponsorship of this project and the creation/maintenance of an FDA compliant medical monitoring program for the three clinical sites in the Phase 2 study, which was executed to plan and has since finished with the closeout of the study last Fall. As a result, the Phase 2 data will be permissible for inclusion in the “burden of proof” submission for our ultimate new FDA 510k approved indication. In the process of pre-determining IDE status for the Phase 2 study, the FDA laid out a clear road-map to successful FDA approval, which included the Phase 2 study per plan and an interventional study to follow. We are currently seeking funding for this required 2<sup>nd</sup> clinical trial, which falls outside of our original Statement of Work for this grant. Upon completion of this required 2<sup>nd</sup> trial, Nonin, Inc will be positioned to submit for a new indication for use for the Equanox 7600 family of oximeters.

5e: Insure mandatory reporting to SAMMC, ISR & USAMRMC is maintained – Completed.

**TASK 6. Future Research Endeavors**

The main outcome of this task is to start the next step in the development and validation of NIRS for diagnosis of ACS. Based on results from the animal and clinical studies included under this award, clinical guidelines for the use of NIRS for the diagnosis and treatment of ACS will be developed and validated. The next step is to plan and conduct a prospective, clinical trial to calculate the sensitivity and specificity of NIRS to diagnose ACS using a series of comparative benchmarks. We designed this study during period 4 and a BAA pre-proposal was written and submitted to USAMRMC. We are



hopeful for the continued funding and support needed to leverage the lessons learned to date to convert moneys and time spent to date into a fieldable solution that will meet the critical unmet need that was at the heart of this project.

## **PROBLEM AREAS**

### **Delayed delivery of final dataset from CRO**

A final closeout visit by Cynthia Donovan of USAMMDA was scheduled for September 30<sup>th</sup> 2013, but due to the government shutdown was delayed by a month. Monitoring of the completed data collection forms needed to take place prior to sending the final forms to our CRO for entry and query generation. Although the queries were received and returned by the first week in December the original delay was exacerbated by the December and January holidays. The final weeks of quarter 2 produced the final, locked dataset after many weeks of reconciliation between the USAMMDA and CRO adverse event databases, as well as final edits to the Data Management Plan. This delay has had a ripple effect on the timeline for analysis of this dataset.

### **Complex Data, Lengthy Analysis**

Major work was put in in the third quarter to identify analysts with the experience and skill-sets necessary to complete an analysis of this magnitude. With agreements now in place, initial analysis has begun. However, it became clear after a set-back of several months that the amount and complex nature of the data being processed would now require an extended timeline to fully complete. In order to allow time for the detail-oriented approach required in this analysis project, as well as time to process this data into publishable results, we requested a 12 month no-cost extension to allow analysis to continue through 31 August 2015 and is currently awaiting approval.

## **KEY RESEARCH ACCOMPLISHMENTS**

1. Close-out visit completed in Quarter 1
2. Manuscript accepted in Quarter 1
3. Data Analysis has begun
4. Animal study abstract submitted in Quarter 4

## **REPORTABLE OUTCOMES**

### **Manuscript**

1. Roskosky M, Robinson G, Reisman W, Ziran B, Shuler M, Freedman B. Subcutaneous Depth in a Traumatized Lower Extremity. *Journal of Trauma and Acute Care Surgery*. (In-press)

### **Abstract**

1. Reisman W, Cole A, **Roskosky M**, Shuler M, Andras L, Moore T. *Near-Infrared Spectroscopy in the Sub-Acute Setting of Lower Extremity Trauma*. 2014 Military Health Systems Research Symposium, August 2014. (Podium)

## **CONCLUSIONS**

The major tasks under this award have been completed. The remaining tasks, including data analysis, manuscript preparation, and presentation of results, have begun and will continue throughout the remainder of the performance period and will require a no-cost extension for completion.

## **REFERENCES**

None.

## **APPENDIX**

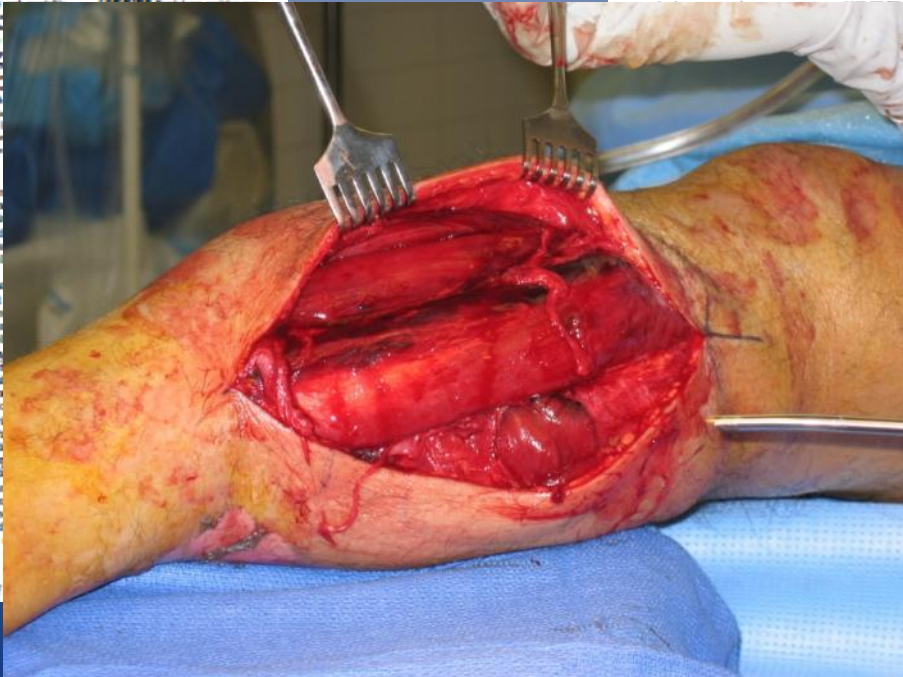
MHSRS Abstract Presentation

# DR080018: The NIRS Research Project

## MHSRS 2014 Meeting: **Next Steps**



PI's: LTC Brett Freedman, MD  
Michael Shuler, MD  
*August 19, 2014*



# Technology Defining Studies

## Clinical: Feasible!

- Uninjured like compartment is ideal control
- Spatial Isolation – NIRS measures the compartment under it
- Nonin is the only oximeter NOT affected by skin color
- SubQ over leg even in the most obese is <2-3cm (98% <2cm)
- SubQ thickness is NOT affected by trauma
- Ambient light does NOT affect Nonin rSO2

## Animal: Accurate!

- NIRS excellent correlation with perfusion pressure
- NIRS bumps after complete fasciotomy, not incomplete
- rSO2 injured > uninjured = uncomplicated injury
- rSO2 injured =/< injured = critical hypoperfusion
- rSO2 bumps occurs even after 8hrs of ACS

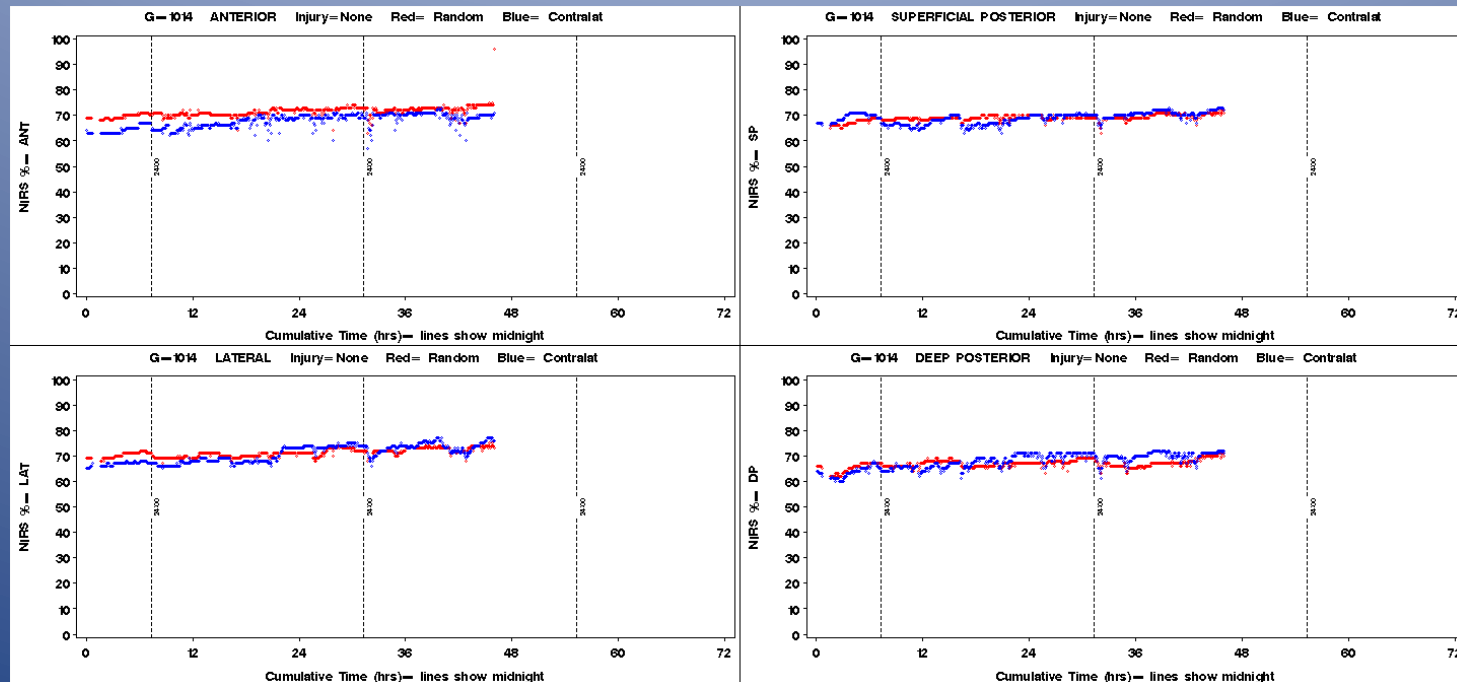
# 4-Year Conclusion

- ACS is a devastating problem that represents a critical unmet need in combat casualty care (*and civilian sector*)
- We are closer today than we have every been to developing and validating a technological solution to this age-old problem. No other group is performing this type of work.
- NIRS oximetry represents the most likely opportunity for success
- Iterative studies like the one presented today are needed to clearly define the ideal technology and method for applying NIRS to diagnose ACS.
- If we don't fund continued R&D for this promising technology, then we will be no closer to a technological solution than we were in 2005-2008
- Our iterative burden of proof approach will win over universal peer buy-in, when we are able to address the remaining technological challenges and complete the validation of this approach. **Success is within reach!!!**

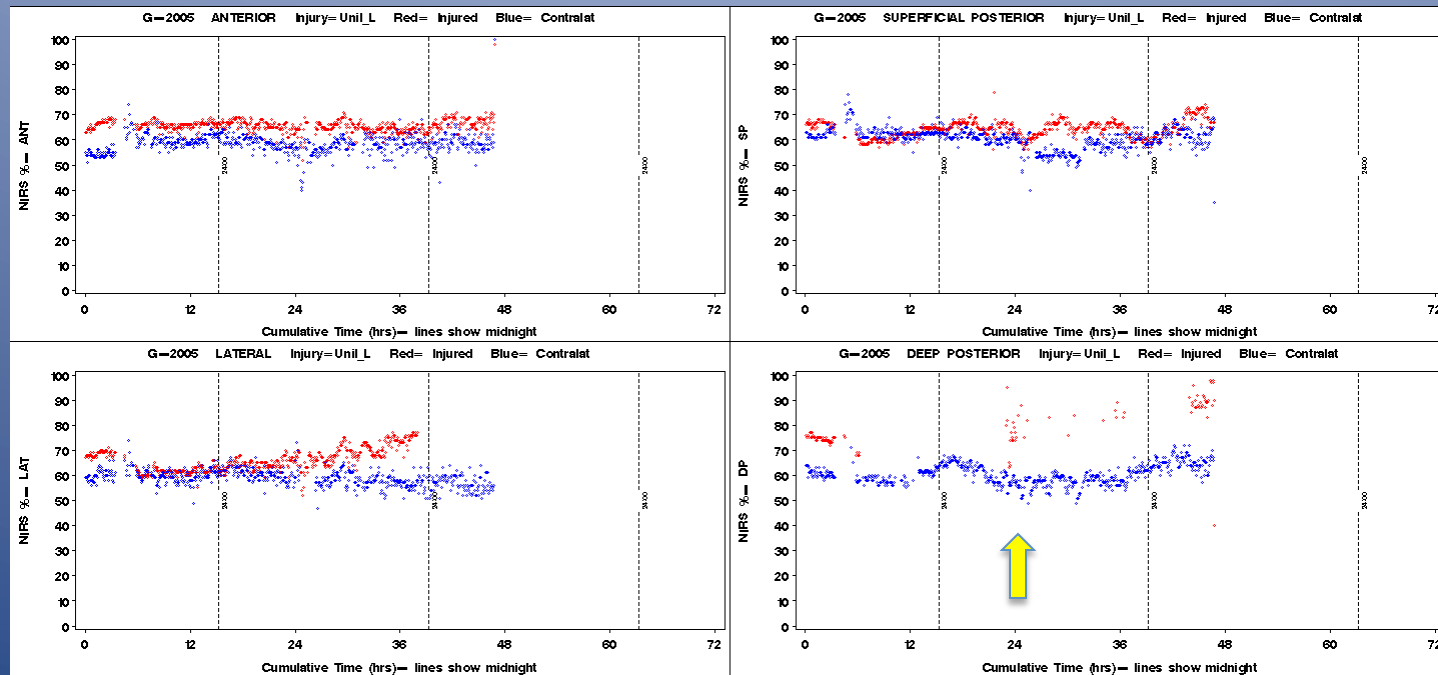


# FDA-IDE – Teaser:

## ICU Control – No Delta



# FDA-IDE – Teaser: Injured, But No ACS → Hyperemia + Drop Data





# FDA-IDE – Teaser:

## Table of Data – 1<sup>st</sup> 5 Minute Data

**Table 1. Summary NIRS values for Unilateral Injured and Uninjured group - Initial Values\***

Unilateral Injured						Uninjured					
		Compartment						Compartment			
		Anterior	Lateral	Deep Post.	Superficial Post.			Anterior	Lateral	Deep Post.	Superficial Post.
Injured Leg	N	57	56	54	51	"Test" Leg**	N	23	22	22	23
	MED	72	72	78	72		MED	69	69	71	72
	MIN, MAX	54, 100	60, 94	61, 98	50, 84		MIN, MAX	62, 94	60, 89	60, 91	64, 83
	MEAN	73	72	79	72		MEAN	70	71	72	72
	STD	9.7	7.1	8.7	6.9		STD	7.2	6.6	8.0	6.0
Uninjured Leg	N	57	56	54	51	Contralateral Leg	N	23	22	22	23
	MED	68	67	70	70		MED	70	71	70	72
	MIN, MAX	53, 87.5	58, 85	56, 90	57, 90		MIN, MAX	55, 87	64, 83	60, 91	60, 94
	MEAN	67	67	71	70		MEAN	70	71	71	73
	STD	7.1	6.6	7.1	6.4		STD	7.2	5.3	7.3	7.6
Difference	N	57	56	54	51	Difference	N	23	22	22	23
	MED	4	5	8	3		MED	-1	-1	1	-1
	MIN, MAX	-24.5, 33	-7, 26	-11, 30	-18, 15		MIN, MAX	-7, 10	-6, 6	-5, 11	-11, 5
	MEAN	5	5	8	1		MEAN	0	-1	1	-1
	STD	9.1	7.5	8.7	7.0		STD	4.9	3.1	3.3	3.3
Mean Diff		5.4	5.1	8.2	1.5	Mean Diff		0.0	-0.6	1.1	-0.9
(95% CI)		(3.0, 7.8)	(3.1, 7.1)	(5.8, 10.5)	(-0.5, 3.4)	(95% CI)		(-2.1, 2.1)	(-2.0, 0.8)	(-0.4, 2.5)	(-2.3, 0.5)
p-value		<.0001	<.0001	<.0001	.143	p-value		1.000	.381	.148	.217

\* Method: Representative 5 minute samples of continuous monitoring were selected and the median of q 4 second NIRS value measurements was used as the summary value. The first five minutes after initiation of monitoring and connection of all leads was selected, unless there was excessive artifact of the sample was otherwise unrepresentative. Modifications of the sample location were decided by graphical and visual analysis of the data. We aimed to sample all compartments at the same time, but if that was not possible individual compartments were sampled at different times. Left and Right legs of the same compartment were always sampled at the same time however. Criteria for the initial measurement were: earliest viable data simultaneously available for both test and control compartment within 8 hours after initiation of monitoring (data are otherwise missing for the compartment).

\*\* Randomly selected

**Hyperemia confirmed with Nonin – on the magnitude of 5%**  
**No difference between like compartments in uninjured critically ill patients**

# FDA-IDE – Teaser:

## Table of Data – 36-48hr Data

**Table 2. Summary NIRS values for Unilateral Injured and Uninjured group - 36-48 Hours after initiation of monitoring\***

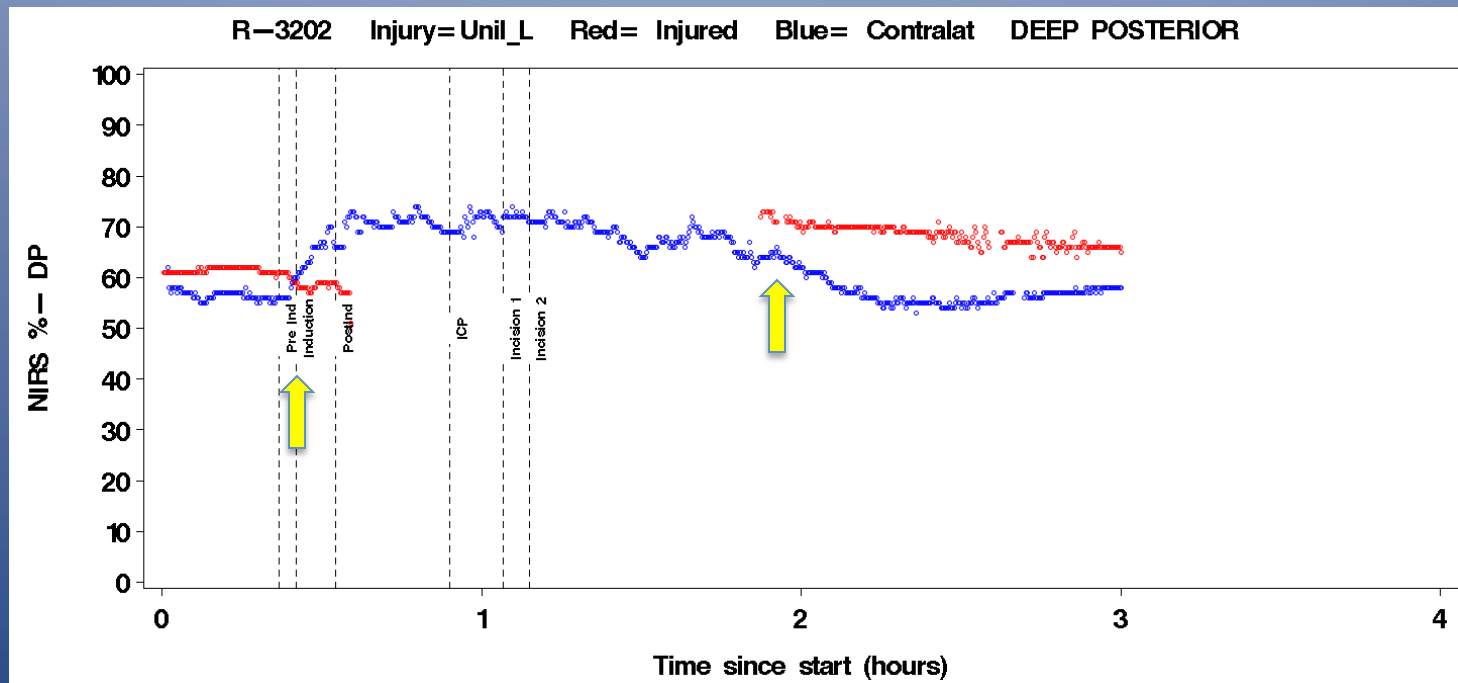
Unilateral Injured					Uninjured				
		Compartment					Compartment		
		Anterior	Lateral	Deep Post.			Anterior	Lateral	Superficial Post.
Injured Leg	N	27	27	19	35	"Test" Leg**	N	15	15
	MED	73	71	80	73		MED	70	69
	MIN, MAX	58, 88	63, 96	60, 96	58, 89		MIN, MAX	58, 75	58, 75
	MEAN	73	73	77	74		MEAN	69	69
	STD	6.9	7.5	9.3	6.8		STD	5.0	4.9
Uninjured Leg	N	27	27	19	35	Contralateral Leg	N	15	15
	MED	67	66	65	71		MED	71	70
	MIN, MAX	50, 85	57, 79	57, 79	57, 78		MIN, MAX	58, 79	59, 77
	MEAN	66	67	67	70		MEAN	70	70
	STD	7.8	6.4	6.9	5.2		STD	5.8	4.6
Difference	N	27	27	19	35	Difference	N	15	15
	MED	6	5	8	4		MED	-2	-1
	MIN, MAX	-4, 22	-5, 23	-5, 26	-5, 18		MIN, MAX	-8, 4	-5, 3
	MEAN	7	6	10	4		MEAN	-1	-1
	STD	6.5	5.4	7.8	5.5		STD	3.4	2.7
<b>Mean Diff</b>		6.6	6.2	9.9	4.5	<b>Mean Diff</b>		-1.2	-0.9
<b>(95% CI)</b>		(4.0, 9.1)	(4.1, 8.4)	(6.1, 13.7)	(2.6, 6.3)	<b>(95% CI)</b>		(-3.1, 0.7)	(-2.4, 0.6)
<b>p-value</b>		<.0001	<.0001	<.0001	<.0001	<b>p-value</b>		.189	.229

\* Method: Representative 5 minute samples of continuous monitoring were selected and the median of q 4 second NIRS value measurements was used as the summary value. The latest time available closest to 48 hours after initiation of monitoring and connection of all leads was selected, unless there was excessive artifact or the sample was otherwise unrepresentative. Modifications of the sample location were decided by graphical and visual analysis of the data. We aimed to sample all compartments at the same time, but if that was not possible individual compartments were sampled at different times. Left and Right legs of the same compartment were always sampled at the same time however. Criteria for the 36-48 hour measurement were: 1. Patient with NIRS data recordings through at least 36 hours after initiation were included (intermittent data ok); 2. The latest viable data simultaneously available for both test and control compartment were sampled, but no earlier than 34 hours after initiation of monitoring (data are otherwise missing for the compartment). Range of times included are 34-49 hours after start of monitoring.

\*\* Randomly selected

**Peak Hyperemia takes time to evolve – on the magnitude of 5-10%  
Uninjured like compartments remain within 1% over 48hrs**

# FDA-IDE – “Golden Ticket”: ACS – Cross-Over + Rebound



# State of Affairs

- Compiled unmatched, substantial, rigorous scientific burden of proof
- There is a technology gap that may exclude up 20% of patients
- This is a NUISSANCE, not a FALSE NEGATIVE – worst case scenario today, is that surgeons would have to resort to current clinical diagnosis methods in upwards of 20% of patients
- When you get a reading on the Nonin oximeter, the number is real
- When you control enough co-factors (i.e. animal models and human controls) – the number is reliable
- We know the missing link for the technology gap, we just need time and resources to develop the answer to the “low light” problem

# Next Steps:

- Fund BAA proposal (or similar) submitted Aug '13
  - Complete development work on ideal sensor specific to ACS
  - Validate sensor in ON-GOING (no-cost to Govt) study at Grady
  - Complete FDA mandated: prospective, diagnostic clinical trial calculating the sensitivity and specificity of NIRS to Dx ACS
  - Develop guidelines determined in previous steps to articulate a NIRS-based diagnostic algorithm submittable to FDA
- Opportunity for “2 for 1” – NIRS clinical study can share resources with minimal marginal cost and also clinically validate a novel NPWT dressing designed to address unmet military needs also funded by CCCRP. Place dressing on fasciotomy wounds (irrigation vs. none).